

## SOME THERMODYNAMIC STUDIES ON PARACETAMOL -CITRIC ACID BINARY DRUG SYSTEM

H. Shekhar\* and Raj Laxmi

Department of Chemistry, V.K.S. University,  
Ara – 802 301, Bihar, Patna, India.

### ABSTRACT

The solid-liquid equilibrium study of binary drugs has been a significant worth for enhanced pharmaceutical properties as compared to the parent drug. The present communication presents some thermo dynamic and interfacial study of paracetamol (PCM) and citric acid (CA) binary drugs. Some thermodynamic quantities such as partial and integral excess entropy ( $S^E$ ), excess enthalpy ( $h^E$ ) excess Gibbs energy ( $g^E$ ) of eutectic and non eutectic mixtures were calculated by the help of activity co-efficient data and the value of  $g^E$  in the system shows the positive deviation from ideal behavior due to stronger association between like molecules during formation of binary mix. On the other hand the negative value of Gibbs free energy of mixing ( $\Delta G^M$ ) favours the mixing for eutectic and non eutectic dispersions is spontaneous. The quantity affecting interfacial properties; Interfacial energy ( $\sigma$ ) grain boundary energy, roughness parameter ( $\alpha$ ) and entropy of fusion per unit volume ( $\Delta S_V$ ) of binary solid dispersion have been highlighted. The size of critical nucleus of binary drug products at different under cooling found in nano scale which may be a big achievement for pharmaceutical industries.

**Keywords:** Binary drug, Interfacial Energy, excess and mixing thermodynamic function.

### INTRODUCTION

The Pharmaceutical dosage of drugs<sup>1-4</sup> is the preliminary and pre-formulation inclusive for designing new drug requires detailed physical, chemical and mechanical properties of the formulation constituents. Binary drug based on hydrophilic excipient can boost the long term stability of the solid dosage form, as well as the drug bioavailability, therapeutic efficacy and safety profile. In addition, the interactions between drug and excipients can get sublimated crystallization profile quality and formulation properties such as the solubility of the mixture, colour, odor and taste of the drug. The thermodynamics studies are very useful for the analysis of drug/excipient interactions during the development of new binary formulation and related technique for classical solid dosage forms (e.g. powders, tablets and capsules). The stability and compatibility of binary drugs may be investigated by the study of phase transformation, melting point and

enthalpy changes. NSAID (Non-Steroidal Anti-inflammatory Drugs) drugs<sup>5-8</sup> have been used as analgesic decongestant, anti-histaminic, anti-cough, pain and fever. Moistures content has important role in commercial medicinal powders for molecular mobility and chemical reactivity. In addition, paracetamol may be sensitive to hydrolytic degradation due to presence of amide group. Recently researches on medicinal products<sup>9-11</sup> at different temperatures and humidity had reported that physical properties of paracetamol in powder form and solution remain unaffected after three months. It is different in the case of Citric acid's stability which decreases with increased temperature sun exposure and pH. It is well tolerated and having of lacks of many side effects of aspirin, so it is commonly used for the relief of fever, headaches, minor aches, pains and severe pain. It also allows lower dose of additional non-steroidal anti-inflammatory drugs for minimizing overall side

effect. Paracetamol is a widely used analgesic and antipyretic while citric acid may act both as an antioxidant or pro-oxidant depending on the concentration.

Citric acid has a wide variety of application due to high solubility, low toxicity and palatability in the food and beverage industry (70%), in pharmaceuticals (12%) and mother industrial application (18%). It can also inhibit nitrification and hence is of interest as a component of Liquid complex fertilizers. Citric acid, a common metabolite of plants and animals, emulsifier, preservative, flavorant, sequestrant and buffering agent has been widely used in various industries especially in cosmetic, food, beverage, pharmaceutical and nutraceutical sector. It plays central role in the metabolism of all aerobic organisms. Due to its remarkable physico-chemical properties and environmentally being nature, it is used currently in flourishing as testified for example by new published<sup>12-16</sup>. As co-builder with Zeolites, it forms concentrated liquid detergents and acts as phosphate builders. It is applied to crosslink a number of significant materials including ultrafine protein fibers for biomedical application, polycol for making biodegradable starchy films. Citric acid polymerized with glycerol forms a thermoset resin, soluble in water, showing several important properties like quick degradable materials. It also acts as excellent harmless disinfection and against several viruses including human norovirus and to reduce micro biological activity. Keeping in view of better therapeutic response of Paracetamol (PCM) and Citric Acid (CA), the present PCM-CA binary system has been aimed for emphasizing thermodynamic and interfacial studies such as solid-liquid equilibrium, excess and mixing thermodynamic functions, activity and activity coefficient, interfacial energy, driving force of solidification and critical radius.

#### EXPERIMENTAL DETAIL

Binary drug dispersions were prepared in sample form by mixing of different ratios of drug (PCM) and excipient (CA) in glass test tube by repeated heating and chilling in ice. For measuring the solid-liquid equilibrium data of the drug dispersions, mixtures of different compositions of the melting temperatures of solid dispersions were determined sincerely by the thaw-melt method using in a Toshniwal melting point apparatus using a precision thermometer which could read correctly up to  $\pm 0.1^\circ\text{C}$ . The literature value<sup>17</sup> of enthalpy of fusion of Paracetamol and Citric Acid was used in determining the various thermodynamic parameters of the binary system.

## RESULT AND DISCUSSION

### SLE Study

The solid liquid equilibrium (SLE) data of solid dispersions of PCM-CA system is reported in Table-1. The binary system forms a eutectic (E)<sup>18</sup> and non-eutectics solid dispersion (A1-A6). The melting point of PCM (M.P. -  $168.7^\circ\text{C}$ ) decreases on the addition of second component CA (M.P. -  $154^\circ\text{C}$ ).

The value of heat of fusion of binary solid dispersions A1-A6 and E has been calculated by mixture law and reported in Table-1. The activity coefficient and activity of components for the systems under investigation has been calculated from the equation<sup>19</sup> given below

$$-\ln\chi_i\gamma_i = \frac{\Delta H_i}{R} \left( \frac{1}{T_e} - \frac{1}{T_i} \right) \quad (1)$$

where  $\chi_i$  and  $\gamma_i$  is mole fraction and activity coefficient of the component  $i$  in the liquid phase respectively.  $\Delta H_i$  is the heat of fusion of component  $i$  at its melting point  $T_i$ .  $T_e$  is the melting temperature of alloy and  $R$  is the gas constant.

### Mixing Functions

The values of activity and activity coefficient of the components evaluate the mixing and excess thermodynamic functions. The partial and integral thermodynamic mixing functions such as molar free energy of mixing ( $\Delta G^M$ ), molar entropy of mixing ( $\Delta S^M$ ) and molar enthalpy of mixing ( $\Delta H^M$ ) of the binary solid dispersions were determined by using the following equations

$$\Delta G^M = RT(\chi_{\text{PCM}} \ln a_{\text{PCM}} + \chi_{\text{CA}} \ln a_{\text{CA}}) \quad (2)$$

$$\Delta S^M = -R(\chi_{\text{PCM}} \ln \chi_{\text{PCM}} + \chi_{\text{CA}} \ln \chi_{\text{CA}}) \quad (3)$$

$$\Delta H^M = RT(\chi_{\text{PCM}} \ln \gamma_{\text{PCM}} + \chi_{\text{CA}} \ln \gamma_{\text{CA}}) \quad (4)$$

$$G_i^{-M} = \mu_i^{-M} = RT \ln a_i \quad (5)$$

where  $G_i^{-M}$  ( $\mu_i^{-M}$ ) is the partial molar free energy of mixing of component  $i$  (mixing chemical potential) in binary mix. The negative value<sup>20</sup> of molar free energy of mixing of alloys (Table 2) suggests that the mixing in all cases is spontaneous. The integral molar enthalpy of mixing value corresponds to the value of excess integral molar free energy of the system favors the regularity in the binary solutions.

### Excess Functions

For unfolding illustration behind the nature of the interactions between the components

forming the eutectic and non-eutectic solid dispersions, the partial and integral excess thermodynamic functions such as integral excess integral free energy ( $g^E$ ), excess integral entropy ( $s^E$ ) and excess integral enthalpy ( $h^E$ ) were calculated using the following equations

$$g^h = RT (\chi_{PCM} \ln \gamma_{PCM} + \chi_{CA} \ln \gamma_{CA}) \quad (6)$$

$$S^E = -R \left( Z_{PCM} \ln \gamma_{PCM} + Z_{CA} \ln \gamma_{CA} + Z_{PCM} T \frac{\delta \ln \gamma_{PCM}}{\delta T} + Z_{CA} T \frac{\delta \ln \gamma_{CA}}{\delta T} \right) \quad (7)$$

$$h^E = RT \left( \chi_{PCM} \frac{\delta \ln \gamma_{PCM}}{\delta T} + \chi_{CA} \frac{\delta \ln \gamma_{CA}}{\delta T} \right) \quad (8)$$

$$g_i^{-E} = \mu_i^{-E} = RT \ln \gamma_i \quad (9)$$

where  $g_i^{-E}$  ( $\mu_i^{-E}$ ) excess chemical potential or excess partial free energy of mixing; The values of  $\delta \ln \gamma_i / \delta T$  can be determined by the slope of liquidus curve near the alloys. The values of the excess thermodynamic functions of binary product reported in Table 3. The value of the excess free energy measures an appreciable deviation from ideal behavior. These thermodynamic data substantiate the earlier evidence of a plausible interaction between the parent components during the formation of binary product. The positive  $g^E$  value<sup>21,22</sup> for all eutectic and non-eutectic solid dispersions infers stronger interaction between like molecules in binary mix. The excess entropy results due to the change in configurational energy due to a change in potential energy and indicates an increase in randomness.

### The Solid-Liquid Interfacial Energy ( $\sigma$ )

Solid-liquid interfacial energy ( $\sigma$ ) evaluated from melting enthalpy change<sup>23</sup> was found comparable in good way with the observed experimental values. The interfacial energy of binary solid dispersions was determined by using Turnbull empirical relationship<sup>24</sup> is expressed as :

$$\sigma = \frac{C \Delta H}{(N)^{1/3} (V_m)^{2/3}} \quad (10)$$

where  $V_m$  is molar volume,  $N$  is the Avogadro's constant and the coefficient  $C$  lies between 0.33 to 0.35 for nonmetallic system.

The value of the solid-liquid interfacial energy of Paracetamol and Citric Acid was found to be  $4.53 \times 10^{-02}$  and  $6.89 \times 10^{-02} \text{ J m}^{-2}$  respectively and for other solid dispersions was mentioned in Table 1. The solid liquid interfacial energy ( $\sigma$ ) has also been determined by using the value of Gibbs-Thomson coefficient. The theoretical basis of determination was made for equal thermal conductivities of solid and liquid phases for some transparent materials.

### Gibbs-Thomson Coefficient ( $\tau$ )

For a planer grain boundary on planer solid-liquid interface the Gibbs-Thomson coefficient ( $r$ ) for the system can be calculated by the Gibbs-Thomson equation and is expressed as

$$\tau = r \Delta T = \frac{T V_m \sigma}{\Delta H} = \frac{\sigma}{\Delta S_v} \quad (11)$$

Where  $r$  is the radius grooves of interface and  $\Delta T$  is the dispersion in equilibrium temperature.  $\tau$  was also determined by the help of Gunduz and Hunt numerical method<sup>25</sup> for materials having known grain boundary shape, temperature gradient in solid and the ratio of thermal conductivity of the equilibrated liquid phases to solid phase ( $R = K_L / K_S$ ). The Gibbs-Thomson coefficient for PCM, CA and their solid dispersions are found in the range of  $8.12 - 8.33 \times 10^{-06} \text{ Km}$  and is reported in Table-1.

### Interfacial Grain Boundary Energy ( $\sigma_{gb}$ )

A considerable force is employed at the grain boundary groove in anisotropic interface. Interfacial grain boundary is conceptualize in a very similar way to nucleation of materials on surfaces during liquid-solid transformation. The interfacial grain boundary energy ( $\sigma_{gb}$ ) was observed using a numerical method<sup>26</sup> without applying the temperature gradient for the grain boundary groove shape. The grain boundary energy can be obtained by the equation:

$$\sigma_{gb} = 2\sigma \cos \theta \quad (12)$$

where  $\theta$  is equilibrium contact angle precipitates at solid-liquid interface of grain boundary. At zero contact angle the grain boundary energy could be twice the solid-liquid interfacial energy in the present case. The value of  $\sigma_{gb}$  for solid PCM and CA was found to be  $9.07 \times 10^{-2}$  and  $13.79 \times 10^{-2} \text{ Jm}^{-2}$  respectively and the value for all solid dispersions is given in Table 1.

### The Effective Entropy Change ( $\Delta S_v$ )

Both volume fraction of phases in mixture and  $\Delta S_V$  the effective entropy change are inter linked to unfold the interface morphology during solidification. The entropy of fusion ( $\Delta S = \Delta H/T$ ) value (Table - 1) is calculated by heat of fusion values of the materials. The effective entropy change per unit volume ( $\Delta S_V$ ) is given by

$$\Delta S_V = \frac{\Delta H}{T} \cdot \frac{1}{V_m} \quad (13)$$

Where  $V_m$  is the molar volume of solid phase.  $\Delta H$  is the enthalpy change and  $T$  is the melting temperature. The value of  $\Delta S_V$  are reported in Table – 1 and entropy of fusion per unit volume ( $\Delta S_V$ ) for PCM and CA was found 543 and 849  $\text{kJK}^{-1}\text{m}^{-3}$  respectively.

### The Driving Force of Nucleation ( $\Delta G_V$ )

The Gibbs free energy during growth of crystalline solid is generated due to change in enthalpy, entropy and specific volume and non-equilibrium leads. The driving force for liquid-solid transition cumulatively occurs due to the difference in Gibb's energy between the two phases. The solidification process have been previously discussed on the basis of diffusion model, kinetic characteristics of nucleation and on thermodynamic features. The lateral motion of rudimentary steps in liquid leads stepwise and non-uniform surface at low driving force while continuous and uniform surface advances at sufficiently high driving force. The driving force of nucleation from liquid to solid during solidification ( $\Delta G_V$ ) can be determined at different undercoolings ( $\Delta T$ ) by using the following equation<sup>27</sup>

$$\Delta G_V = \Delta S_V \Delta T \quad (14)$$

$\Delta S_V$  is opposed by the increase in surface free energy due to creation of a new solid-liquid interface. The solid phase nucleates as small spherical cluster of radius arising due to random motion of atoms within liquid. The value of  $\Delta G_V$  for each solid dispersions and pure components are shown in the Table- 4.

### The Critical Radius ( $r^*$ )

Rapidly dispersed transient unstable (embryos) on under cooling liquid becomes saturated and provides stable embryo of a critical size with radius  $r^*$  for nucleation. It was determined by the Chadwick relation<sup>28</sup>

$$r^* = \frac{2\sigma}{\Delta G_V} = \frac{2\sigma T}{\Delta H_V \Delta T} \quad (15)$$

where  $\Delta H_V$  is the enthalpy of fusion of the compound per unit volume and  $\sigma$  is the interfacial energy respectively. The critical size of the nucleus for the components and eutectic and non eutectic solid dispersion was calculated at different undercoolings and values are presented in Table 5. It was found that the size of the critical nucleus decreases with increase in the undercooling of the melt. The existence of embryo and a range of embryo size can be expected in the liquid at any temperature. The value of  $r^*$  for pure components (PCM and CA) and solid dispersions lies between 43 to 166 nm at undercooling 1 – 3.5 °C.

### Critical Free Energy of Nucleation ( $\Delta G^*$ )

A localized activation/critical free energy of nucleation ( $\Delta G^*$ ) is latent factor<sup>29</sup> and responsible to form critical nucleus of the materials.

$$\Delta G^* = \frac{16\pi\sigma^3}{3\Delta G_V^2} \quad (16)$$

The value of  $\Delta G^*$  for alloys and pure components has been found in the range of  $10^{-15}$  to  $10^{-16}$  J per molecule at different undercoolings, and has been reported in Table 6.

### Interface Morphology

Growth morphology developed during phase transformation is combined effect of thermodynamics kinetics, crystal structures and interfacial sciences. The solid-liquid interface has been predicted from the value of the entropy effusion. According to Hunt and Jackson<sup>30</sup>, the type of growth from a binary melt depends upon a factor  $\alpha$ , is presented as:

$$\alpha = \xi \frac{\Delta H}{RT} = \xi \frac{\Delta S}{R} \quad (17)$$

where  $\Delta S/R$  (Jackson's roughness parameter  $\alpha$ ) is the entropy of fusion (dimensionless) and  $R$  is the gas constant,  $\xi$  is a crystallographic factor depending upon the geometry of the molecule and has a value less than or equal to 1. When  $\alpha$  is less than two the solid-liquid interface is atomically rough and exhibits non-faceted growth. The value of Jackson's roughness parameter ( $\alpha$ ) given in Table -1 has been found greater than 2 which indicate the faceted<sup>31</sup> growth proceeds in the entire solid dispersion.

**CONCLUSION**

The phase diagram of PCM-CA system confirms the formation of simple eutectic type dispersion. The thermodynamic mixing and excess functions  $\Delta G^M$  and  $g^E$  values for eutectic and non-eutectics solid dispersion are being found positive which infers the non

spontaneous mixing in all cases and there is stronger association between like molecules.

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**Table 1 : Phase Composition, melting temperature, values of entropy of fusion per unit volume ( $\Delta S_v$ ), heat of fusion ( $\Delta H$ ), interfacial energy ( $\sigma$ ), grain boundary energy ( $\sigma_{gb}$ ), Gibbs-Thomson coefficient ( $\tau$ ) and roughness parameter ( $\alpha$ )**

Alloy	$\chi_{PCM}$	MP	$\Delta H$ (J/mol)	$\Delta S$ (J/mol/K)	$\alpha$	$\sigma \times 10^2$ (J/m <sup>2</sup> )	$\sigma_{gb} \times 10^2$ (J/m <sup>2</sup> )	$\Delta S_v$ (kJ/m <sup>3</sup> /K)	$\Delta H_v$	$\tau \times 10^6$ Km
A1	0.1	151	40375	95.224	11.453	66.631	133.262	826.733	350.535	8.0595
A2	0.2	147.3	38900	92.552	11.132	64.267	128.534	805.079	338.375	7.9826
A3	0.3	142.3	37425	90.115	10.838	61.903	123.806	885.449	326.197	7.8812
A4	0.4	137.4	35950	87.597	10.536	59.539	119.078	765.095	313.995	7.7819
E	0.515	123.2	34253.75	86.455	10.398	56.820	113.640	957.026	299.934	7.5056
A5	0.8	158.7	30050	69.608	8.372	50.083	100.166	613.701	264.935	8.1608
A6	0.9	163.6	28575	65.448	7.872	47.719	95.438	578.547	252.594	8.2480
PCM		168.7	27100	61.353	7.379	45.356	90.712	543.853	240.220	8.3397
CA		154	41850	98.000	11.788	68.995	137.990	849.351	362.673	8.1232

**Table 2: Value of partial and integral missing of Gibbs free energy ( $\Delta G^M$ ), enthalpy ( $\Delta H^M$ ) and entropy ( $\Delta S^M$ ) of PCM-CA system**

Alloy	$\Delta G_{PCM}^{-M}$ J/mol	$\Delta G_{CA}^{-M}$ J/mol	$\Delta G^{-M}$ J/mol	$\Delta H_{PCM}^{-M}$ J/mol	$\Delta H_{CA}^{-M}$ J/mol	$\Delta H^{-M}$ J/mol	$\Delta S_{PCM}^{-M}$ J/mol/k	$\Delta S_{CA}^{-M}$ J/mol/k	$\Delta S^{-M}$ J/mol/k
A1	-2.1154	-3.5251	-3.384	8114.863	370.139	1144.611	19.143	0.875	2.701
A2	-2.0969	-5.5944	-4.894	5622.448	775.751	1745.090	13.380	1.855	4.160
A3	-3.4528	-3.7980	-3.694	4153.723	1229.198	2106.555	10.009	2.965	5.078
A4	-5.4627	-3.4120	-4.232	3122.040	1740.153	2292.907	7.618	4.247	5.595
E	-6.3607	-6.2619	-6.312	2180.632	2378.272	2276.487	5.517	6.016	5.759
A5	-5.7462	-2.1538	-5.027	796.792	5774.948	1792.423	1.855	13.380	4.160
A6	-3.6298	-2.1782	-3.484	381.138	8356.012	1178.625	0.875	19.143	2.701

**Table 3: Value of partial and integral excess Gibbs free energy ( $g^E$ ), enthalpy ( $h^E$ ) and entropy ( $s^E$ ) of PCM-CA system**

Alloy	$g_{PCM}^{E}$ J/mol	$g_{CA}^{E}$ J/mol	$g^E$ J/mol	$h_{PCM}^{E}$ J/mol	$h_{CA}^{E}$ J/mol	$h^E$ J/mol	$s_{PCM}^{E}$ J/mol/k	$s_{CA}^{E}$ J/mol/k	$s^E$ J/mol/k
Al	8114.863	370.139	1144.611	122352.676	-25229.821	-10471.571	269.428	-60.377	-27.396
A2	5622.448	775.751	1745.090	46334.894	-22490.155	-9525.145	96.863	-57.734	-26.814
A3	4153.723	1229.189	2106.555	20691.892	-21364.414	-8747.522	39.822	-54.403	-26.135
A4	3122.040	1740.153	2292.907	7907.700	-18510.720	-7943.352	11.660	-49.344	-24.942
E	2180.632	2378.272	2276.487	-1758.472	-14940.618	-8151.812	-9.942	-43.712	-26.320
A5	796.792	5774.948	1792.423	-7732.003	35621.572	938.712	-19.756	69.137	-1.977
A6	381.138	8356.012	1178.625	-9490.957	116626.243	3128.763	-22.611	247.984	4.448

**Table 4: Value of volume free energy change ( $\Delta G_V$ ) during solidification for PCM-CA system of different undercoolings ( $\Delta T$ )**

Alloy $\Delta T \rightarrow$	$\Delta G_V$ (J/cm <sup>3</sup> )					
	1.0	1.5	2.0	2.5	3.0	3.5
Al	0.826	1.239	1.652	2.065	2.478	2.891
A2	0.805	1.207	1.610	2.212	2.415	2.817
A3	0.785	1.177	1.570	1.962	2.355	2.747
A4	0.765	1.147	1.530	1.912	2.295	2.677
E	0.757	1.135	1.514	1.892	2.271	2.649
A5	0.613	0.919	1.226	1.532	1.839	2.145
A6	0.578	0.867	1.156	1.445	1.734	2.023
PCM	0.544	0.816	1.088	1.360	1.632	1.904
CA	0.849	1.273	1.698	2.122	2.547	2.971

**Table 5: Critical size of nucleus ( $r^*$ ) at different undercoolings ( $\Delta T$ )**

Alloy $\Delta T \rightarrow$	$r^*$ (nm)					
	1.0	1.5	2.0	2.5	3.0	3.5
Al	161.18	107.45	80.59	64.47	53.72	46.05
A2	159.64	106.42	79.82	63.85	53.21	45.61
A3	157.62	105.08	78.81	63.04	52.54	45.03
A4	155.62	103.74	77.81	62.24	51.87	44.46
E	150.10	100.06	75.05	60.04	50.03	42.88
A5	163.20	108.80	81.60	65.28	54.40	46.62
A6	164.96	109.97	82.48	65.98	54.98	47.13
PCM	166.78	111.18	83.39	66.71	55.59	47.65
CA	162.46	108.30	81.23	64.98	54.15	46.41

**Table 6: Value of critical free energy of nucleation ( $\Delta G^*$ ) for alloys of PCM-CA system at different undercoolings ( $\Delta T$ )**

Alloy $\Delta T \rightarrow$	$\Delta G^* \times 10^{16}$ (J)					
	1.0	1.5	2.0	2.5	3.0	3.5
Al	72.518	32.230	18.219	11.602	8.057	5.919
A2	68.617	30.496	17.154	10.978	7.264	5.601
A3	64.424	29.632	16.106	10.307	7.158	5.259
A4	60.411	26.849	15.102	9.665	6.712	4.931
E	53.632	23.836	13.408	8.581	5.959	4.378
A5	55.866	24.838	13.971	8.941	6.209	4.562
A6	54.393	24.174	13.598	8.702	6.043	4.440
PCM	52.855	23.491	13.213	8.456	5.872	4.314
CA	76.282	33.903	90.070	12.205	8.475	6.227

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